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CASE REPORT

Primary Sclerosing Epithelioid Fibrosarcoma of the Lung in a Patient with Lynch Syndrome

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Abstract Sclerosing epithelioid fibrosarcoma (SEF) is a rare neoplasm arising mostly in limbs and limb girdles, with a high rate of recurrence and a strong tendency to metastasize. This case study is of a 54-year-old woman with an asymptomatic mass in the upper lobe of the left lung detected by PET-CT when staging for Lynch syndrome-associated colon carcinoma. Histology of the resected tumor showed epithelioid cells arranged in nests, partly restiform within a zone of sclerosing fibrosis. Immunohistochemistry was positive for vimentin, epithelial membrane antigen, and S100-protein. Eight months after lung resection, the patient was diagnosed for basal cell carcinoma on her back. At the end of a two year follow-up period, she developed metastases to the mediastinum, vertebrae, ribs, femurs, pelvic bones, kidneys, and one lung, histologically all related to SEF. Here we report the first case of a SEF primarily arising from the lung and discuss it in the context of the current literature.

Keywords Lung · Sclerosing epithelioid fibrosarcoma · Lynch syndrome · Hereditary nonpolyposis colorectal cancer

Introduction

Sclerosing epithelioid fibrosarcoma (SEF) was first described in 1995 by Meis-Kindblom [1]. Subsequently, a number of cases have been reported in the literature showing that these tumors arise as mostly deep-seated in the soft tissue and mainly affect limbs, limb girdles, trunk, head, and neck in young to middle-aged adults [1–4]. The tumor belongs to the group of fibrosing fibrosarcomas, together with low-grade fibromyxoid sarcoma and hyalinizing spindle cell tumor with giant rosettes [2–4]. SEF is reported to have the most aggressive behavior among this group, showing a low-grade histology but having a high incidence of local recurrence and distant metastatic spread [3, 5]. Characteristic pathological features of SEF that are generally recognized comprise small to medium-sized epithelioid cells with clear to eosinophilic cytoplasm and small nucleoli [1, 5]. Immunohistochemistry (IHC) characteristically shows positive vimentin staining; in some cases additional positive staining includes epithelial membrane antigen (EMA), S100-protein, or neuron-specific enolase (NSE) [1, 3]. Therapy of choice is a wide local resection, while the role of systemic treatment remains controversial [3].

Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome is a heritable cancer syndrome associated with colorectal carcinoma and other extracolonic malignant manifestations. Interestingly, the occurrence of various types of sarcomas has also been previously described [6].

Case Report

A 54-year-old woman presented with cramping pain in the right lower abdomen. A colonoscopy and a biopsy revealed an adenocarcinoma of the ileocecal valve. The patient had a positive family history for hereditary nonpolyposis colorectal cancer, Lynch syndrome II, and fulfilled the Amsterdam criteria. Computed tomography of the thorax

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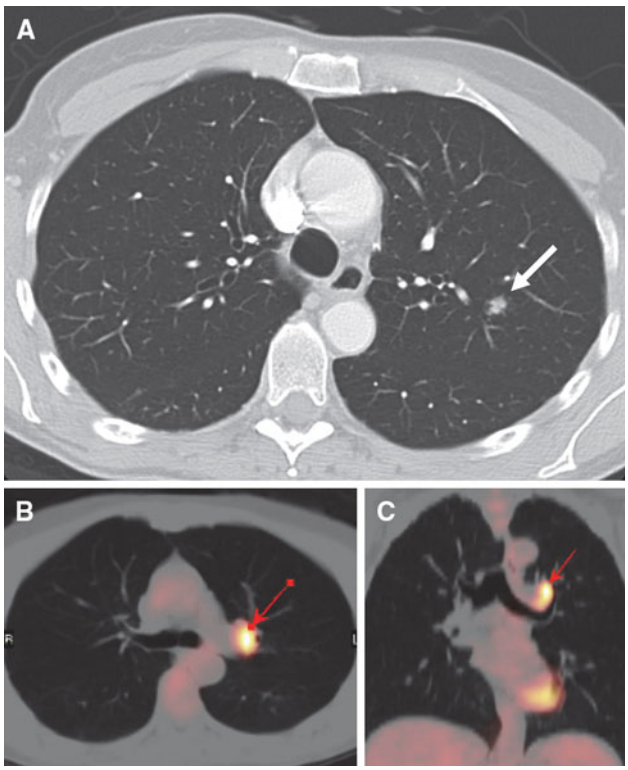

Fig. 1 **a** Computed tomography of the thorax of a 54-year-old female with a round mass in the left upper lobe measuring 2.5 cm. **b**, **c** PET-CT scan shows enlarged FDG-positive ipsilateral hilar lymph nodes while the primary pulmonary tumor is FDG-negative

disclosed a small mass in the upper lobe of the left lung (Fig. 1a, arrow), which was found to be fluorodeoxyglucose (FDG)-negative in the staging PET-CT; however, ipsilateral hilar lymph nodes were enlarged and FDG-positive (Fig. 1b, c, arrow), while the patient was asymptomatic. The colon cancer was completely removed by hemicolectomy, the carcinoma was analyzed for microsatellite instability, and the *KRAS* and *BRAF* genes were sequenced. As five microsatellite instability markers (BAT25, BAT26, D2S123, D5S346, and D17S250) were considered to be unstable, the tumor was thus defined as unstable, but no mutation in the *KRAS* and *BRAF* genes was found. As a diagnostic procedure, the pulmonary tumor was wedge-resected and the hilar and lobar lymph nodes were excised. Frozen section analysis revealed inconclusive results in both specimens. However, the final histological analysis showed a malignant epithelioid tumor; thus, an extended resection as a double sleeve of the left upper lobe was performed due to firmly adherent lymph nodes to the pulmonary artery and bronchus. Lymph nodes were removed from Nos. 5, 10, and 12, of which only lymph nodes No. 12 were also positive for malignant epithelioid tumor. Mediastinal lymph nodes were left in situ in order not to compromise the blood supply of the bronchial anastomosis.

The result of the final histological analysis was sclerosing epithelioid fibrosarcoma, staged pT1b pN1 cM0 with a FNCLCC grade 2, score 5 (3, 1, 1). The pathological specimen displayed sclerosing fibrosis and hyalinosis, partly with mucoid transformation of the stroma (Fig. 2a, b). Within the zones of fibrosis, infiltrates of epithelioid cells were detected, partly in nests and partly restiform arranged, with round to oval nuclei. There was no histologic evidence for metastatic disease of the colon carcinoma. IHC was negative for pancytokeratin B (Fig. 2c, arrow), thyroid transcription factor-1, calretinin, panmelan A, synaptophysin, desmin, estrogen receptor, smooth muscle actin, CD79A, CD20, and CD138, but positive for EMA, faintly for CD10, and focally for progesterone receptor as well as S100-protein. The histology of the lymph nodes was identical to that of the primary tumor (Fig. 3a), with the typical marker pattern for SEF: positive for vimentin (Fig. 3b) and for EMA (Fig. 3c), but negative for pancytokeratin (Fig. 3d). Analysis of the proteins encoded by mismatch repair genes (*MSH2*, *MSH6*, *MLH1*, and *PMS2*) showed positive staining (Fig. 3e, f), which makes an association of SEF with Lynch syndrome less likely.

Meanwhile, the patient received nine cycles of FOLFOX chemotherapy. Eight months after surgery the patient developed a lesion on the back which was removed and histologically showed a multilocular superficial-type basal cell carcinoma. A follow-up PET-CT showed positivity within the fifth lumbar vertebra, left iliac bone, left femur, and mediastinum, and a biopsy from mediastinal lymph nodes and also from bone lesions confirmed metastatic spread from the pulmonary SEF. All osseous metastases were subsequently treated by radiotherapy with curative intent. Accordingly, the mediastinal lymph nodes were also resected in a curative treatment concept. In the same operation, an unexpected lesion in the right upper lobe was also removed, and both specimens were confirmed to be metastases from the SEF.

A follow-up PET-CT a few months later showed further metastatic spread to multiple bone locations as well as to mediastinum and kidneys, while the lung remained tumor-free. At the time of evaluation, the patient was asymptomatic but underwent radiation therapy for extrapulmonary metastases.

Discussion

This case of SEF is unusual for the following aspects: (1) SEF arose primarily from the lung, (2) the patient developed

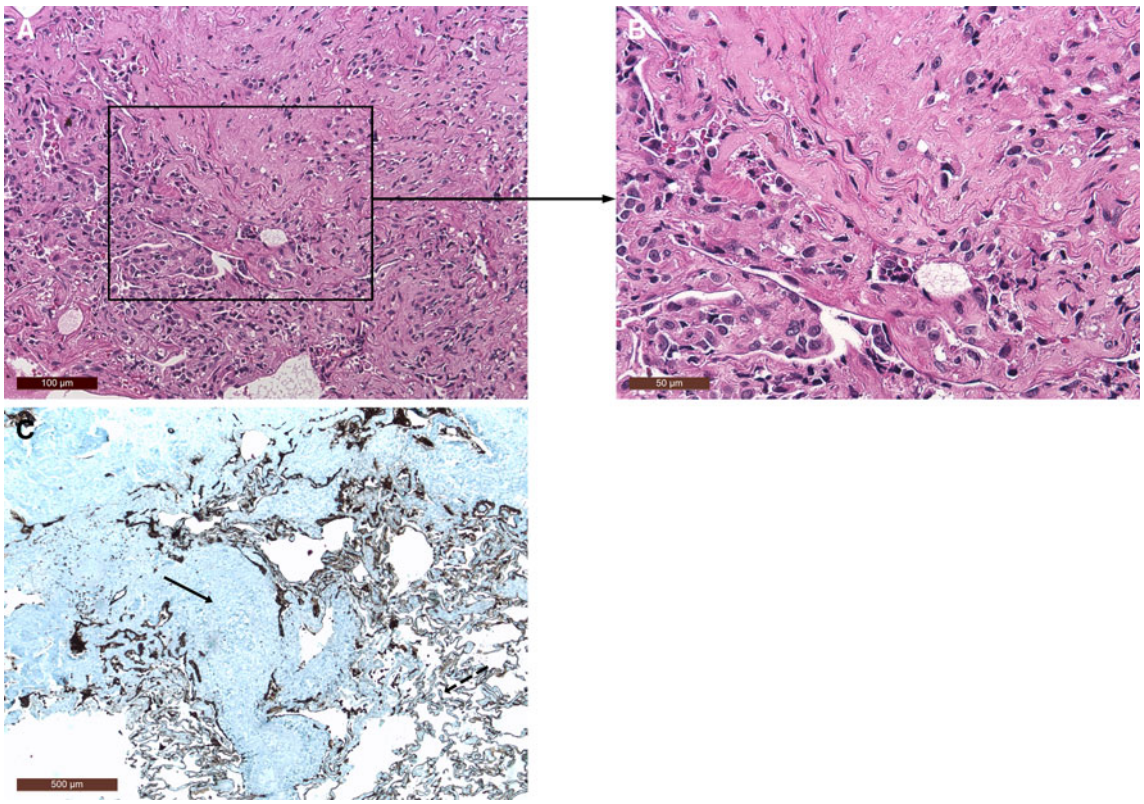

Fig. 2 Representative histology of sclerosing epithelioid fibrosarcoma of the primary pulmonary specimen: Hematoxylin & eosin [H&E, magnification ×100 (**a**) and ×200 (**b**)], showing epithelioid cells, arranged in a restiform manner or in nests, and embedded in a fibrotic matrix. Immunohistochemistry was negative for pancytokeratin within the tumor (**c**, *arrow*), while normal lung tissue showed extensive pancytokeratin staining (*dashed arrow*)

three metachronous tumors of completely distinct histology within a short period of time, (3) SEF and basal cell carcinoma were suspected to be associated with Lynch syndrome.

SEF originating from the lung has not been described as yet as this tumor entity arises mostly from the deep soft tissue of limbs and limb girdles, head, neck, and trunk [3, 4]. However, the histological appearance of SEF in our patient is in accordance to the reported literature, showing dense collagenous stroma with small to medium epithelioid cells arranged in cords and strands, staining positive for vimentin. Surprisingly, the primary tumor within the lung was FDG-negative, possibly due to the low metabolic activity of fibrous tumors in general [7]. Surprisingly, hilar lymph nodes were proven to be tumor-free but showed a strong FDG signal, most likely due to unspecific inflammation.

Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome is an autosomal dominant multiorgan cancer syndrome that emerges in individuals with mutations in DNA mismatch repair (MMR) genes, e.g., *hMLH1* or *hPMS1*. Loss of function of the MMR system leads to the accumulation of DNA replication errors in the HNPCC-associated tumors. This phenomenon is also known as microsatellite (MS) instability [8]. The most frequent malignancy in individuals with Lynch syndrome is colorectal cancer. Among many tumor entities, fibrosarcoma, skin cancer, and several types of lung cancer were described in HNPCC mutation carriers or patients meeting the Amsterdam criteria [9–11]. Lynch syndrome-associated tumors can show a loss of immunohistochemical staining for the protein encoded by the mutated MMR gene [8]. The tumor in our patient showed normal staining for all four proteins analyzed, which makes an association with the Lynch syndrome less likely.

A possible association between tumors of the skin and HNPCC is described with regard to Muir-Torre syndrome [9, 12]. There is only one published case of a patient who suffered from colorectal cancer and various skin cancers, including basal cell carcinoma [13].

According to the literature, between 30 and 50 % of SEF patients had local relapse between two to five years after initial diagnosis [1, 3–5]. In contrast, except for one metastasis in the upper right lobe, the lung of this patient remained disease-free. Therefore, a radical local resection treatment is justified and should be recommended for primary lung SEF.

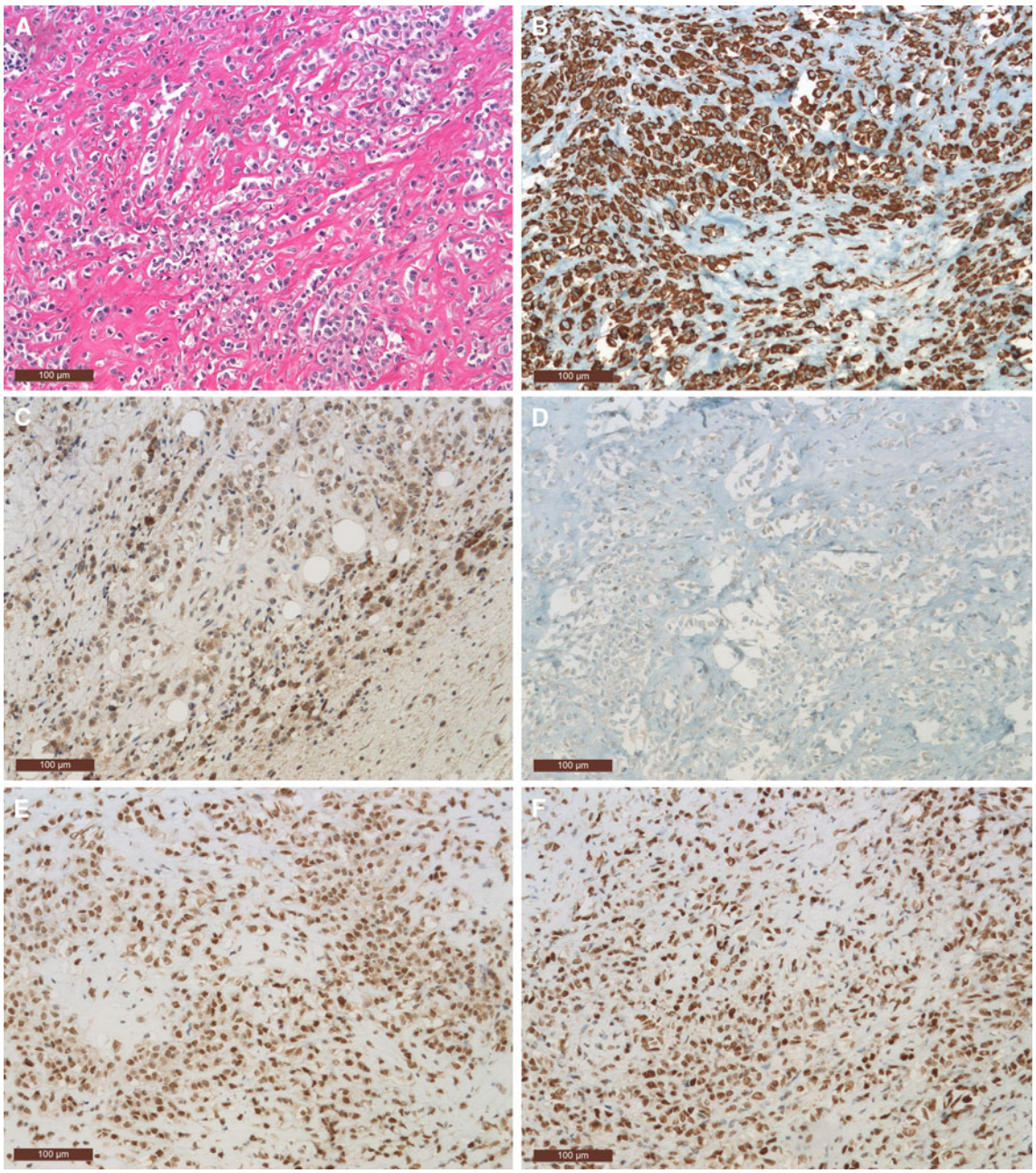

Fig. 3 Histology and immunohistochemistry from metastatic lymph nodes. Hematoxylin & eosin (H&E) shows extensive fibrotic tissue with scarce remaining normal lymph node architecture (**a**). Vimentin was strongly positive (**b**) and there were considerable amounts of epithelial membrane antigen (EMA) expressed (**c**), while pancytokeratin was absent (**d**) (magnification ×100). All cells showed an equal distribution of normal nuclear staining for MLH1 (**e**) and MSH2 (**f**)

Conflict of interest The authors have no conflicts of interest or financial ties to disclose.

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